

SEVENTH REPORT OF THE DIRECTOR

NATIONAL INSTITUTE OF DIABETES AND DIGESTIVE AND KIDNEY DISEASES

B E T T E R H E A L T H



T H R O U G H R E S E A R C H

Front cover

A focus on basic research has traditionally guided NIDDK's programs. Advances in the type of laboratory studies shown here underlie much of the Institute's clinical studies. These may deal with the health implications of obesity or with improved patient care, or self-care in diabetes. The ultimate focus of NIDDK research is improving the quality of medical care—and the quality of life for the patient.

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Preface

As the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) begins to celebrate its 40th Anniversary, we are pleased to present this Seventh Report of the Director. The Institute is responsible for research on a wide spectrum of diseases affecting virtually every family in the nation. These diseases are among the most common, chronic, disabling and costly facing us; they afflict millions of Americans of all ages, backgrounds and economic circumstances and constitute a tremendous drain in terms of human suffering and economic costs.

This Seventh Report describes the numerous and impressive research advances of the last two years, the opportunities they opened up for further research and the plans developed to meet future needs. It is our hope that the research advances chronicled here will contribute to the achievement of our common goal—to create the knowledge which will make possible better diagnosis, treatment and prevention of the diseases for which our Institute bears responsibility.

This report would not be complete without a warm acknowledgement of the tireless work, dedication and skills of the scientists who conducted these studies, and the many interested citizens and their representatives who made this work possible.



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Director
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*National Institute of
Diabetes & Digestive &
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40TH ANNIVERSARY 1950–1990

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National Institute of Diabetes and Digestive and Kidney Diseases

Introduction

Since its establishment as a separate Institute at NIH four decades ago, the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) has steadily expanded its research efforts in the prevention, diagnosis, and better medical management of a wide range of mostly chronic disorders. Several of these diseases are among the leading causes of disability and death in the Nation; all affect seriously the quality of life of those suffering from them. Their collective economic burden exceeds \$100 billion annually; the cost of these diseases in terms of human suffering cannot be measured.

The outlook for advances in the treatment and prevention of these diseases depends on basic and clinical investigations into the nature of their interference with the normal functioning of the body's many complex systems. These diseases include diabetes and endocrine and metabolic disorders, including cystic fibrosis, digestive diseases and nutritional disorders, and kidney and urinary tract diseases and blood disorders. Basic research is conducted and supported in areas such as endocrinology, genetics, metabolism, biochemistry, physiology, molecular biology, pathology, and pharmacology.

NIDDK supports basic and clinical research through investigator-initiated grants, program project and center grants, and career development and training awards. It also supports research and development projects and large-scale clinical trials through grants, contracts, and cooperative agreements. The Institute's Division of Intramural Research conducts basic studies in endocrinology; genetics; chemistry; biochemistry; metabolism; physical, chemical, and molecular biology; chemical physics; pharmacology; and pathology. Its scientists also conduct clinical research on diabetes, other metabolic diseases, cystic fibrosis, endocrine disorders, digestive diseases, kidney diseases, and blood disorders.

To carry out its mission, NIDDK supports research and training projects in more than 400 non-Federal institutions. Intramural basic and clinical research is also conducted on and near the NIH reservation in Bethesda, Maryland, and at field stations in and near Phoenix, Arizona.

Research Focus—Trans-NIDDK Programs

Overview

Trans-NIDDK programs are those activities common to several Divisions and Branches and requiring



Basic laboratory studies undergird all biomedical research.

NIDDK-wide participation. Many considerations have converged to make this new focus of activity necessary, including the interrelated nature of NIDDK programs, the interdisciplinary nature of much of the Institute's research, the significant role of minority health issues in NIDDK programs, the strengthening of the Institute's activities in epidemiology research and in analysis and planning related to national population surveys, the development of new multidisciplinary NIH inter-Institute programs such as AIDS research and the mapping of the human genome, and the new forms and directions of NIDDK collaboration with industrial research and development teams.

Program Development Highlights

Interdisciplinary Research

Interrelated subject areas are best illustrated by Institute activities related to diabetic kidney disease and obesity.

Kidney Disease of Diabetes Mellitus. Kidney disease of diabetes mellitus is a devastating complication of diabetes for which no effective treatments or preventive measures exist. To attack this problem, the Institute has embarked upon a major multifaceted initiative, mobilizing intramural and extramural expertise to conduct basic and clinical research studies. A study has already been launched of the epidemiology and natural history of kidney disease of diabetes mellitus in the Pima Indians in Arizona, who have the world's highest frequency of noninsulin-dependent diabetes. Additionally, ongoing evaluation of patients in the Diabetes Control and Complications Trial will help determine the relationship between degree of

blood sugar control and development of early kidney complications in insulin-dependent diabetes.

Obesity. In recognition of the high prevalence and the physical and mental health consequences of obesity, NIDDK is considering a major prevention initiative that will build on the research to date.



NIDDK intramural research has traditionally emphasized basic research.

Minority Health Issues

Many of the diseases and conditions for which the Institute is responsible affect minority groups disproportionately. The following programs focus on minority health issues.

Patterns of Disease and Disease Prevention.

An effort is under way to stimulate biomedical and epidemiologic research to determine why minority populations in the United States, particularly those of Hispanic, black, Native American, and Asian/Pacific Islander heritage, suffer disproportionately from specific diseases and to work toward correcting these disparities.

Training and Targeted Support. Programs of research training and targeted support are designed to enhance research capabilities in minority scientists and institutions.

Epidemiology Program

Epidemiologic research is being pursued and strengthened in an effort to increase the store of knowledge about the diseases within the purview of the Institute.

Research Coordination and New Initiatives.

An NIDDK/National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) Epidemiology Coordinating Committee serves to stimulate staff research and coordinate Institute and interagency efforts, emphasizing cooperative programs with the National Center for Health Statistics (NCHS).

NCHS Population Surveys. The National Health and Nutrition Examination Survey (NHANES) involves interviews, physical examinations, and diagnostic and biochemical testing of a representative sample of Americans. The National Health Interview Survey is the principal source of information on the health of the civilian noninstitutionalized population of the United States. Data are collected through a personal household interview. These surveys will provide an opportunity to investigate, in an unbiased sample of the U.S. population, certain aspects of NIDDK-studied diseases, including prevalence and etiology. The Institute provides financial and technical support to NCHS for this purpose.

NIH Inter-Institute Programs

Multidisciplinary NIH inter-Institute programs are best illustrated by NIDDK activities related to AIDS research and to the mapping of the human genome.

AIDS and Human Immunodeficiency Virus Research. Intramurally and extramurally, NIDDK is contributing to the national effort against AIDS. Many of the disease and emphasis areas within the mission of the Institute are directly relevant to AIDS, including gastroenterology and nutrition, endocrinology, chronic and end-stage renal disease, urology, and hematology.



Basic research may involve experimental animals.

The Human Genome. Past Institute accomplishments encompass mapping and sequencing insights into gene regulation and expression and progress toward gene therapy. NIDDK research has led to the sequencing and cloning of many important genes, including those that code for insulin, erythropoietin, human growth hormone, and many hormone receptors, as well as genes affected by metabolic diseases

such as Lesch-Nyhan syndrome, Fabry's disease, and Tay-Sachs disease. In addition, NIDDK scientists have greatly narrowed the search for genes that are critical to insulin-dependent diabetes, cystic fibrosis, polycystic kidney disease, and other diseases that have a major impact on public health.

Biotechnology

Industrial groups often contribute to facilitating research and clinical trials. The NIH makes available research information and advances under several technology transfer programs, including patent development activities that benefit industry and the public. In addition to these, the Institute joins with industrial R&D teams in the following cooperative biotechnology ventures.

Milk Protein Gene Expression. Many proteins used as pharmaceuticals such as tissue plasminogen activator and clotting factors VIII and IX must be isolated from natural sources or produced in tissue culture and are only available in limited quantities. NIDDK intramural researchers collaborated with industrial researchers to develop a genetic engineering (transgenic) technique that has great potential for the large-scale production of such drugs in the milk of animals. A gene promoter specific for the mammary gland is fused to human DNA encoding the desired protein. The product is injected into fertilized eggs still at the one-cell stage, some of which will develop into mature animals producing the desired protein in their milk. Such an animal passes this ability on to its offspring and is not hurt in any way by the harvesting of the protein.

Erythropoietin Cloning and Production for the Treatment of Anemia. In chronic renal disease, the kidney cannot make enough of the hormone erythropoietin to keep up the body's supply of red blood cells, and anemia results. The gene responsible for regulating erythropoietin biosynthesis has been identified, cloned, and inserted into cultured cells. These cells subsequently are able to produce the natural hormone in sufficient amounts for large-scale distribution of erythropoietin for clinical use. Treatment of chronic renal disease patients with erythropoietin eliminates the need for blood transfusions and vastly improves the quality of life of these patients. This cooperative effort between the Institute and biotechnology firms has led to a major medical achievement. Now that erythropoietin is available in adequate quantities, it is being tested in other conditions; experimental data from animal studies show that erythropoietin may cause an increase in the production of the fetal type of hemoglobin. Preliminary tests are under way in sickle cell patients who are

already receiving the drug hydroxyurea to see if erythropoietin causes an additive effect.

Research Focus—Diabetes, Endocrinology, and Metabolic Diseases

Overview

The Division of Diabetes, Endocrinology, and Metabolic Diseases (DDEM) supports extramural research related to diabetes and its complications, endocrinology and a variety of endocrine disorders, and metabolism and metabolic diseases, including cystic fibrosis.

Highlights of Research Advances

The following section briefly highlights a few of the areas in which DDEM has reported recent progress in its research programs.

Exploring the Cause of Insulin-Dependent Diabetes Mellitus

Insulin-dependent diabetes mellitus (IDDM) is now recognized as being an autoimmune disease. Advances have been made in human studies looking for key immune mechanisms underlying the onset of IDDM. Researchers supported by NIDDK had previously shown that patients with IDDM have antibodies to a protein molecule found only on the insulin-secreting beta cell of the pancreas. Their hypothesis is that this protein is the primary target against which the body mistakenly makes antibodies that trigger the destruction of beta cells. These researchers reported evidence supporting this hypothesis from a study of newly diagnosed patients with IDDM. These patients had been followed for several years previously as "at-risk" siblings of a twin or triplet with IDDM. Antibodies to the protein were detected in serum samples that preceded the clinical onset of IDDM by several years. If a reliable marker can be shown to forecast the onset of IDDM, then it may be possible to arrest the loss of beta cells and prevent the onset of IDDM.

Cell Receptors for Insulin: Structure and Function

Sequencing of the gene for the human insulin receptor has led to significant understanding of how the receptor functions. An alpha subunit of the protein binds the insulin at the cell surface, which transmits a message to a beta subunit crossing the cell membrane and possessing an enzymatic (kinase) function in the cytoplasm. Evidence from three extramural and intramural NIDDK-supported laboratories has now demonstrated the essential role of the kinase in the implementation of insulin's message to the cell. By modification of the gene, it was shown that binding

of insulin is not enough to ensure that the receptor will allow insulin to act. Defects have been demonstrated in rare human types of diabetes that involve the translation of the gene's instructions for the receptor, its insertion in the cell membrane, or its actual structure. These defects manifest as extreme resistance to insulin.



Unfortunately, "insulin-dependent diabetes" means just that . . . every day. Hopefully, NIDDK's research effort will change this in the future.

Inhibin: A New Hormone of Fundamental Importance

Inhibin is a newly isolated gonadal hormone that selectively inhibits the secretion of the pituitary's follicle stimulating hormone (FSH); FSH regulates reproductive function in the ovaries and testes. Inhibin is composed of an alpha and a beta chain of amino acids. Its inhibitory effect on FSH is opposed by a hypothalamic hormone, FSH-releasing protein (FRP), which is similar in structure (made up of two inhibin beta chains) and stimulates FSH secretion. Inhibin and FRP are now being shown to have a regulatory role in other important systems, including growth hormone and ACTH secretion. These peptides appear to regulate blood cell differentiation. The inhibin alpha-beta dimer and the FRP (or "activin") beta-beta dimer are structurally related peptide dimers with opposing effects. Formation of such dimers is a novel mechanism for generation of hormone structural diversity through subunit combinations.

Development of Obesity: Low Metabolic Rate Is a Risk Factor

Intramural NIDDK research among southwestern American Indians (the Pima Indians) has established that resting metabolic rate is a familial trait. This finding extended the evidence of a genetic role in obesity observed in extramural studies among adopted compared with biological children of the parents and

among twins compared with others in the same family. Using a metabolic chamber equipped as living space, the intramural team has now measured 24-hour energy expenditure over a 2-year followup period and has found that those with the lowest resting metabolic rates gained the most weight. In fact, the resting metabolic rate was found to predict the gain in body weight over a 4-year followup period. Thus, a low rate of energy expenditure may contribute to the occurrence of obesity in families because a lower energy requirement makes it that much easier to overeat. This may explain how obesity can occur even if the total food intake is no greater or even less than that seen in those remaining at normal weights.

Adipsin: Fat Cell Enzyme in Blood May Regulate Lipid Metabolism in Obesity and Differentiate Metabolic Abnormalities From Obesity Due to Overeating

Recently, new and potentially important gene products of the adipose cell have been identified. One such product is adipsin, a protein whose amino acid sequence classifies it as a protein-degrading enzyme, or protease, with a signaling function.

Adipsin is efficiently secreted by fat cells and is found in the bloodstream in abundant amounts. It is a candidate for an adipostat, that is, a systemic signaling molecule involved in regulating lipid metabolism and/or energy balance. Experimental evidence shows that adipsin is severely reduced in several forms of obesity, both acquired and genetic, but not in obesity due to overeating. Adipsin is the first fat cell-derived protein discovered that is responsive to nutritional and hormonal stimuli and is therefore a critical signaling molecule that regulates fat cell metabolism. Measurement of the expression rate of the gene coding for adipsin may allow genetic- or metabolic-based obesities to be distinguished from those caused by pure overeating.

Enzyme Replacement Therapy for Rare Inherited Metabolic Disorders

A chemically altered enzyme has been used to treat a severe inherited form of immune deficiency. This may be a prototype for development of similarly altered enzymes for the therapy of other inborn errors of metabolism. Severe combined immunodeficiency disease is caused by an inborn absence of the enzyme adenosine deaminase (ADA). Children afflicted with the disease have little or no immunity to infection. Because repeated infections could prove fatal, treatment is required to restore the immune system. Researchers from a biotechnology company developed a method for the preparation of polyethylene glycol (PEG)-modified enzymes, including PEG-modified bovine ADA (PEG-ADA). Early tests in animals showed that PEG-ADA was

not toxic and was very stable in blood plasma. PEG modification greatly lengthened the effective lifespan of ADA in blood. A clinical study with PEG-ADA to treat human ADA deficiency was then undertaken. In two patients, treatment reversed the biochemical signs of ADA deficiency and after 4 to 6 months increased the number and functioning of their lymphocytes. The two treated children had improved resistance to infection and gained weight.

Cystic Fibrosis: The Search for the Defective Gene

The pattern of inheritance in cystic fibrosis is recessive; a child must inherit a defective gene from both parents to be affected. One in twenty Caucasians carries the defective gene, and 1 in every 1,600 Caucasian children is born with the disease. During 1985, through the research of investigators in three countries, several gene-linkage markers narrowed the location of the CF gene to the middle third of the long arm of chromosome 7, in a region of about 1 million DNA base pairs. These new markers for the CF gene allowed detection of the gene in DNA samples from members of families where there was a known case of CF. The finding of markers closely linked to the CF gene brought closer the actual isolation of the gene itself. In 1987, a genomic sequence close to the CF locus was reported to have been selectively cloned and characterized.

In CF, the body produces a thick, sticky mucus that clogs the lungs and digestive system, interfering with breathing and digestion. It is hoped that isolation of the defective gene responsible for CF will elucidate the underlying biochemical defect responsible for these clinical manifestations. It is also hoped that identification of the CF gene will lead to methods of identifying its asymptomatic carriers and, ultimately, a neonatal screening technique for the general population.

Program Highlights

Diabetes Research Program

- A Consensus Development Conference on Diet and Exercise in Noninsulin-Dependent Diabetes Mellitus was held December 8-10, 1986. The conference panel emphasized the importance of weight loss to therapy.
- The report "Diabetes in Hispanic-Americans" was submitted to Congress.
- Diabetes and Hypertension Program staff actively participated in the Working Group on Hypertension in Diabetes of the National High Blood Pressure Education Program of the National Heart, Lung, and Blood Institute.

- During FY's 1987-88, more than 6,400 diabetes-prone (BB) rats were distributed to researchers.
- The National Disease Research Interchange (NDRI) is procuring and distributing human organs and tissues for biomedical research. With a specific mandate from Congress, the NIH Division of Research Resources has entered into a contract with NDRI to continue its activities.
- The Registry on Pancreas and Islet Cell Transplantation will serve as a research tool for the world community to aid in the development of successful techniques for pancreas and islet cell transplantation.
- During FY's 1987-88, the National Diabetes Advisory Board (NDAB) finished its update of the long-range plan for diabetes.
- The American Diabetes Association conference on Self-Blood Glucose Monitoring was held November 17-19, 1987, and was cosponsored by NIDDK and two other agencies. The panel recommended self-blood glucose monitoring for patients taking insulin but emphasized that more research is needed.

Diabetes Centers Program

Central to the NDAB new long-range plan is a recommendation for Diabetes Interdisciplinary Research Centers to foster collaboration of basic scientists in the new research technologies (molecular biology, immunology, etc.) with diabetes researchers.

Clinical Trials Program

Six new clinical centers were added for phase III of the Diabetes Control and Complications Trial (DCCT); all completed the certification requirements and initiated recruitment of volunteers. The phase III protocol was completed. The most significant changes to the phase II protocol were additions of a clearance test to assess glomerular filtration rate and 24-hour urine collections to enable biochemical assessments of dietary sodium and protein intakes. A novel approach has been centrally instituted to facilitate patient recruitment, using an interactive, computer-assisted telephone answering device that is tied to a toll-free telephone number. This device screens subjects according to the major eligibility criteria, then records the names, addresses, and telephone numbers of potential eligible volunteers who receive additional information on DCCT by mail.

National Diabetes Data Group

- The National Diabetes Data Group (NDDG) has devoted a major effort to planning for an extensive

study of the epidemiology and natural history of diabetes and glucose intolerance in the general population of the United States during the 1988-94 NHANES III of NCHS.

- NDDG has also participated in analysis of the 1980-83 study of Hispanic American populations in the Hispanic HANES survey of NCHS.
- Analysis of the NHANES II survey, the only study of the U.S. population in which oral glucose tolerance tests were employed, continues to be an important NDDG activity.

DDEM/World Health Organization (WHO) Collaborating Center in Diabetes Research

This new Collaborating Center, the first in diabetes in the United States, was officially approved by WHO and the Department of Health and Human Services' Assistant Secretary for Health in 1985. Its functions are to encourage, solicit, and support international research on diabetes.

- The center anticipates conducting an epidemiologic analysis of the WHO Multinational Study on Vascular Disease in Diabetes, by contract.
- The center is participating in an international effort sponsored by WHO, including quantifying mortality associated with the disease, developing guidelines for field studies of diabetes, preparing a document on the worldwide scope and impact of diabetes, identifying and fostering opportunities for training in epidemiology, and standardizing methodologies for the assessment of diabetes complications.

National Diabetes Information Clearinghouse (NDIC)

- The Combined Health Information Database (CHID) provides information about educational materials and projects in diabetes to all health professionals.
- The fourth edition of the NDIC compendium was published in February 1987. This 210-page book is a compilation of educational programs, materials, and selected pilot and feasibility studies in diabetes.

Endocrinology Research Program

- In June 1986, a contract was awarded for the epidemiologic study of the risk of Creutzfeldt-Jakob disease in naturally derived human growth hormone recipients.
- A National Osteoporosis Workshop was jointly sponsored with two other Institutes and the National Osteoporosis Foundation on February 9-11, 1987.
- The Hormone Distribution Program of NIDDK makes available to the research community human and

animal pituitary hormones, antisera against these hormones, and selected other hormonal and biological products. Most of these products are unavailable commercially. Surveys of endocrinology research published in major endocrinology journals reveal that hormones supplied through this program were used in half of these studies.

- The Steroid Reference Collection, located at Westfield College, London, is a research resource comprising standard samples of approximately 5,000 steroids, most of which are not available commercially.

Metabolic Diseases Branch

- The Metabolic Diseases Branch (MDB) and the Division of Life Sciences, Los Alamos National Laboratory, have developed a resource for mapping DNA probes by hybridizing radiolabeled DNA probes to dot-blots of separated and purified human chromosome on nitrocellulose filters. A program announcement has invited applicants to submit DNA probes for mapping.
- The MDB planned, organized, and coordinated an "NIH Day" for the National Organization for Rare Disorders, Inc., which represents 45 to 50 different rare disease support groups throughout the United States.
- The Fourth International Congress of Inborn Errors of Metabolism was held May 26-30, 1987, in Sendai, Japan. Branch staff assisted in the organization and coordination of this congress.
- An international Workshop on Crystal Growth of Biological Macromolecules was held July 19-25, 1987, in Strasbourg, France. The branch cosponsored the travel of five young scientists to this international workshop.

Cystic Fibrosis Research Program

- The NIDDK and the Canadian Cystic Fibrosis Foundation jointly sponsored "The 6th Professional Conference: Broken Arrow," in Ontario, November 12-15, 1986. The objective of the meeting was to bring together scientists working in the forefront of CF research and to discuss their work with clinicians treating CF patients.
- The NIDDK, NHLBI, and the Cystic Fibrosis Foundation cosponsored a workshop on the "Clinical-Behavioral Aspects of Cystic Fibrosis: Directions for Future Research."
- A workshop cosponsored by the Cystic Fibrosis Foundation on "Cell Immortalization Approaches for Cystic Fibrosis Research" was held in Bethesda, Maryland, in April 1987.

Program Development Activities

Program Announcements

- Small Grants To Facilitate Use of New Molecular Biologic and Genetic Techniques by Researchers in Diabetes, Endocrinology, and Metabolic Diseases.
- Small Grants on Somatic Cell Transfer of Genes Associated With Specific Metabolic and Endocrine Disease.
- Bone Active Hormones and Cytokines (with NIAMS).
- Research on the Etiology and Functional Consequences of Nonmalignant Endocrine Tumors.
- Small Grants for Crystallization of Membrane Transport Systems Relevant to Inherited Metabolic Disorders.

Planned Program Announcement Initiatives

- Resources for Mapping of DNA Probes (Interagency Agreement with Department of Energy).
- Neuroendocrinology of Human Stress.
- Training Protein Crystallographers.
- Resource for Structural Studies of Biological Macromolecules.
- New Approaches to the Analysis of Complex Genomes (NIH-wide PA).
- Computer-Based Representation and Analysis of Molecular Biology Data (NIH-wide program).

Requests for Proposals and Requests for Applications

- Support of the National Hormone and Pituitary Program.
- Extraction and Purification of Rat Pituitary Hormones, 1987.
- Immunoaffinity Purification of Human Pituitary Hormones was issued to prepare human pituitary hormones that approach 100-percent purity with regard to contamination by other pituitary hormones.
- The Genetic and Metabolic Defects Underlying Cystic Fibrosis was released with a receipt date of March 1987.

Other Program Initiatives for FY 1988

- Implementation of the National Long-Range Plan to Combat Diabetes.
- Basic and Clinical Approaches to the Therapy and Understanding of Rare Metabolic Disorders.
- Expansion of the CF Centers Program.

- Enhancement of Clinical Application of Advances in Fundamental Endocrinology.
- RFA's for Grants to Study Hypertension in Diabetes.
- Enhancement of Research Training in Diabetes, Endocrinology, and Metabolism.
- Strengthening of NIDDK's Hormone Distribution Program.
- Application of New Molecular/Cell Biologic Techniques to the Study of Metabolic Processes.
- Clinical Trials of New Therapeutic Modalities in Diabetes, Endocrinology, and Metabolic Diseases.

Research Focus—Digestive Diseases and Nutrition

Overview

The Division of Digestive Diseases and Nutrition (DDDN) has responsibility for managing research programs related to liver and biliary diseases, pancreatic diseases, and gastrointestinal diseases, including neuroendocrinology, motility, immunology, digestion in the gastrointestinal tract, nutrient metabolism, obesity, eating disorders, and energy regulation.

The third, or Special Projects Branch, includes the Research Training and Career Development Program; the Research Centers Program, comprising both Digestive Diseases Centers and Clinical Nutrition Research Units; the U.S.-Japan Malnutrition Panel; the National Digestive Diseases Information Clearinghouse; and the Epidemiology and Digestive Diseases Data Base System.

Highlights of Research Advances

The following section briefly highlights some of the areas in which DDDN has reported recent progress in its research programs.

Digestive Diseases

Duodenal Ulcer: The Role of Impaired Bicarbonate Secretion. Each year in the United States there are approximately 300,000 new cases of duodenal ulcer, about 3.2 million recurrences, and 3,000 deaths due to the disease. In spite of the high prevalence and inherent economic costs of duodenal ulcer, estimated at about \$3 billion annually, the precise pathophysiologic factors responsible for it are not fully understood. In animals and humans, the duodenal mucosa secretes bicarbonate. Epithelial bicarbonate production, along with the overlying layer of mucus, provides a barrier to protect the mucosa from injury by luminal acid and pepsin. Bicarbonate secretion was measured in a group of healthy subjects and a group of patients with inactive duodenal ulcer disease. Results

indicated that upper duodenal mucosal bicarbonate secretion is significantly below normal at rest and in response to luminal acidification in patients with duodenal ulcer. Impaired mucosal bicarbonate secretion by the duodenal bulb may be an important factor in the pathogenesis and the frequency of recurrence of duodenal ulcer.



Clinical studies of antiulcer drugs involve periodic, direct observation of peptic ulcers with an endoscope. This study compares the efficacy of two different drugs.

Gallstones: The Hormonal Basis. In various normal or pathologic states, the contractility of the gallbladder may decrease. This decrease in contractility may allow small crystals of cholesterol and/or other nucleating compounds to remain in the gallbladder and form the nidus for gallstone formation. Although the lipid composition of the bile is a major determinant in whether gallstones will form, it is not the sole determinant. Two recent investigations suggest that hormonal influences may play a major role in gallbladder dynamics and should be investigated in the early stages of gallstone formation. There may be an imbalance that occurs between gallbladder emptying (stimulated by cholecystokinin, or CCK) and gallbladder filling (significantly increased by pancreatic polypeptide) in the gallstone-prone conditions of pregnancy and parenteral hyperalimentation. If so, interventional studies to bring the plasma levels to normal may be attempted. Pilot studies in which CCK is being infused to enhance gallbladder contractility are now being conducted in some pediatric patients on total parenteral nutrition.

Nutrition

Fat Cell Metabolism and Obesity: Neural Control. It has been estimated that 26 percent of U.S. adults, about 34 million persons ages 20 to 75 years, are overweight. With weight change, adipose sites

increase or decrease in size. This is the effect of the balance of lipolysis, which releases fatty acids, and reesterification, which controls the storage of fatty acids as triglycerides within the cell. Lipolysis is at least in part under the control of adrenergic receptors, which are the protein molecules recognizing chemical substances that stimulate the sympathetic nervous system. The several types of adrenergic receptors are demonstrated by the effects of different chemical substances (catecholamines) on the receptors. Two specific types, β_1 and α_2 receptors, predominate in the plasma membranes of human adipocytes. These two receptors have opposing effects on lipolysis: β_1 stimulates, and α_2 inhibits. Lipolytic response to the β -adrenergic agonist, isoproterenol, suggests that although β_1 receptor activity is clearly greater in abdominal than gluteal tissue, there are no sex-related differences at these sites. Response to norepinephrine (which activates both β_1 and α_2 receptors) is greater in the abdominal tissue of the female than the male. Given the apparently equal degrees of β responsiveness in abdominal tissue of males and females, the data for norepinephrine suggest that males have more abdominal α_2 receptor function than females. This difference may partially explain the greater tendency for male subjects to accumulate adipose tissue in the abdominal region. At equal degrees of absolute adiposity, the risk of associated morbidities such as hypertension, stroke, ischemic heart disease, and type II diabetes is greater in individuals with predominantly abdominal as opposed to gluteal fat deposits (high waist:hip circumference ratio).

Fatty Acids Essential for Normal Brain and Eye Function. Essential fatty acids include two families distinguished by the position of the double bond closest to the terminal methyl group of the fatty chain. One family is designated omega-6 fatty acids and includes linoleic acid and its longer derivatives such as arachidonic acid. The other family is known as omega-3 fatty acids and includes linolenic acid and its longer chain derivatives. Omega-3 as well as omega-6 fatty acids are precursors for the synthesis of compounds important in control of physiological function (prostaglandins, prostacyclins, thromboxanes, and leukotrienes). In the past few years, increased attention has been given to the question of the possible health benefits of those omega-3 fatty acids that are abundant in seafood. Epidemiological studies have suggested that increased dietary intake of these omega-3 fatty acids helps to lower plasma cholesterol and is associated with a decreased risk of cardiovascular disease. The mechanisms for exerting these potential health benefits are not fully understood.



NIDDK Clinical Nutrition Research Units engage in nutrition research, stimulate progress in patient care, and as in this case, provide dietary advice and nutrition information to patients and the public.

Despite the lack of a clear demonstration of omega-3 fatty acid deficiency in humans, evidence from animal studies and more recent work in nonhuman primates indicate that omega-3 fatty acids are essential for normal development and functioning of the retina and brain. At present, changes in retinal function provide the best evidence for functional effects of omega-3 fatty acid deficiency in mammals. One of these compounds (docosahexaenoic acid) is the major polyunsaturated fatty acid in the photo receptor membrane of the retina and in cerebral gray matter.

Program Highlights

- The Liver Tissue Procurement and Distribution System (contract) consists of a coordinating center and five tissue collection centers, each of which harvests discarded diseased livers from liver



Studies of obesity involve not only traditional weighing on scales but also measurement of skinfold thickness in various locations of the body with the aid of special, standardized calipers.

transplant patients and makes them available to investigators needing such material for their research.

- PA: "Pancreatitis: Pathogenesis, Diagnosis, and Therapy."
RFA's: "Pathogenesis of Intestinal Dysfunction in AIDS"; "Core Grants for Clinical Nutrition Research Units"; "Conferences on Nutritional and Metabolic Factors in Relation to Aging"; and "Behavioral Aspects of Nutrition."
RFP: "Human Liver Cell Culture Facility."
Sources sought announcement: "Gastrointestinal Epithelial Cell Cultures—Sources Sought."

Conferences and Workshops

- "Toxic Oxygen and the Liver" workshop, September 13-15, 1987, Bethesda, Maryland.
- "Program Emphases and Mechanisms for the Support of Training and Research on Digestive Diseases" workshop, March 31, 1987, Washington, D.C.
- "Campylobacter Gastritis" workshop, July 28-31, 1987, Keystone, Colorado.
- "Gastrointestinal Tract II: Adaptation and Growth," FASEB Summer Research Conference, July 5-10, 1987, Copper Mountain, Colorado.
- "Mechanisms of Chronic Infection and Inflammation in IBD" workshop, October 7-11, 1987, Fort Lauderdale, Florida.
- "Nutrition Science at NIH: Current Research and Mechanisms of Support" workshop, at the Annual Meeting of the American Society for Parenteral and Enteral Nutrition, February 3, 1987, New Orleans, Louisiana.
- "Causes and Consequences of Hypochlorhydria in the Elderly" workshop, September 28-29, 1987, Bethesda, Maryland.

Program Development Activities for FY 1988

Planned Program Announcement Initiatives

- Expansion and Stabilization of DDDN Career Awards.
- Identification of Mechanism for Differences in Development of Obesity.
- Clinical, Physiological, and Psychological Factors Associated With Irritable Bowel Syndrome and Related Disorders in Man.
- Bioavailability and Maximum Safe Intake of Nutrients.

Other Program Initiatives

- Pathogenesis of Intestinal Dysfunction in AIDS.
- Behavioral Aspects of Nutrition in the Development of Obesity and Eating Disorders.
- Prevention of Cholesterol Gallstones.
- Human Liver Cell Culture Facility.
- Drug Therapy of Chronic Disabling Diarrhea.
- Development and Characterization of Intestinal Epithelial Cell Cultures.
- Evaluation of Scientific Evidence Supporting Development of Revised Weight-for-Height Guidelines.
- Establishment of DDDN Nutrition Academic Awards.

Planned Workshop/Conference Initiatives

- Neuropeptide Modulation of Mucosal Immunity.
- Lipid Digestion and Transport.
- Considerations in the Development of Revised Recommended Dietary Allowances.

Research Focus—Kidney, Urologic, and Hematologic Diseases

Overview

The programs of the Division of Kidney, Urologic, and Hematologic Diseases (DKUH) are keyed to important public health problems. They address, among other subject areas, the underlying mechanisms of kidney disease and its progression through studies of normal structure and function of the kidney, including renal metabolic functions, transport, and fluid-electrolyte dynamics; the metabolic and systemic abnormalities of chronic renal disease; and the control of its progressing to end-stage renal failure. Research areas in urology include urinary tract infection, neuromuscular disorders of bladder function, obstruction, urolithiasis (kidney stone disease), and benign prostatic hyperplasia. The Division's Hematology Program supports investigations into basic mechanisms of normal blood cell function and pathogenesis of hematologic disorders, including development of treatment and prevention modalities, clinical application, and evaluation of treatment.

Highlights of Research Advances

The following section briefly highlights a few of the areas in which DKUH has reported recent progress in its research programs.

Blood Pressure Treatment for Diabetic Kidney Disease

Kidney disease of diabetes mellitus, the single most common cause of chronic renal failure in the United States, affects 30 to 40 percent of patients with IDDM. There is evidence that glomerular capillaries show abnormalities in structure from increased glomerular filtration rates (GFR) and raised intraglomerular pressure on a chronic basis. A high GFR has been known to occur in a proportion of diabetics for many years, and recent studies suggest that diabetic patients who have elevated GFR lose glomerular function (at a faster rate than those with normal GFR) and progress to renal failure. Clinical studies have shown that treatment of hypertension in patients with moderately advanced diabetic nephropathy retards subsequent deterioration of renal function, presumably by ameliorating abnormal glomerular capillary hemodynamics. In the experimental diabetic rat, reduction of intraglomerular hypertension, either by administration of an angiotensin I converting enzyme inhibitor (ACEI) or by feeding a diet reduced in proteins, appears to prevent not only the glomerular hyperfiltration and proteinuria but also the renal damage of diabetes, independently of the metabolic disturbance. Other recent results that support these findings include the demonstration that only antihypertensive therapy that directly prevents glomerular capillary hypertension such as ACEI limits glomerular injury in experimental animals.

Kidney Transplantation: New Immunosuppressive Protocols

The past decade has witnessed a dramatic development in the field of kidney transplantation. There are many reasons for this, but the single most important factor is undoubtedly the introduction of cyclosporin A (CsA) as the basic drug of immunosuppression. However, CsA's nephrotoxic side effects continue to be of great concern, and rejection remains the most important etiologic factor resulting in graft loss in patients receiving CsA.

Monoclonal antibodies (Mab's) directed against specific rejection-associated molecules on cell surfaces are under active investigation. To date, the only licensed Mab with clinical utility in renal transplantation is Orthoclone OKT3; it has been demonstrated to be effective in reversing established graft rejection, but it also has important drawbacks.

Immunosuppressive regimens combining CsA and OKT3, and in some cases other agents as well, are under active investigation. These combinations often achieve a high rate of reversal of rejection and, very importantly, a low incidence of recurrent rejection,

subsequent infection, and graft loss. For example, one group of investigators has conducted a pilot study using OKT3[®] antilymphocyte antibody; and a combination of low doses of azathioprine, prednisone, and CsA. There have been no complications thus far except for expected fever and chills. These immunosuppressive treatment regimens attempt to prevent rejection, prolong graft survival, reduce incidence of infection, and shorten hospital stay in kidney transplant patients.



Today in the United States, more than 90,000 patients with kidney failure are being kept alive with the aid of artificial kidneys. This maintenance dialysis therapy evolved through a special NIDDK research program.

Linkage Analysis of Polycystic Kidney Disease

In adult polycystic kidney disease (PKD), the most common heritable renal disease, each offspring of an affected parent has a 50-percent chance of inheriting the gene. The results of studies in nine family pedigrees indicate that the adult PKD locus is closely linked to the alpha-globin locus on the short arm of chromosome 16. Linkage analysis was facilitated by the presence of a "hypervariable" region associated with the alpha-globin locus. This is a small portion of DNA that is repeated back to back hundreds of times on chromosome 16. Additional analyses have shown that the hypervariable marker and the gene resulting in PKD are located close enough on chromosome 16 to be inherited together in approximately 95 percent of cases. In practice, this means that analysis of a family with classic PKD will identify a hypervariable marker of a particular size that is associated with the disease. If a fetus or child from that family carries this particular hypervariable marker, there is a likely chance that he or she will eventually manifest PKD. These studies were carried out on families manifesting the most common phenotype of PKD. They provide the basis for analysis of genetic heterogeneity in the disease. It will be possible to construct a linkage map of chromosome 16 by using polymorphic DNA probes

that have been isolated from chromosome 16 libraries. This genetic map should provide a framework for the physical mapping of the adult PKD locus and through the identification of "bracketing markers" offer a reliable means of prenatal and presymptomatic diagnosis.

Urologic Diseases

Benign prostatic hyperplasia (BPH) is extremely common in the adult male population. BPH can be expected to increase dramatically as the percentage of our population older than 50 increases and the life expectancy of adult males is prolonged. Prostatic growth factor (PrGF) has been isolated from human BPH tissue and subsequently purified; it also has been found in normal adult prostates and in prostatic adenocarcinoma. It is hypothesized that PrGF may contribute to the development of fibrostromal nodules characteristic of human BPH as well as bony metastasis observed in prostatic cancer. The exact role that PrGF may have in BPH and its interaction with androgens known to affect the prostate remain to be elucidated.

When a matching kidney is available, transplantation can give renal failure patients a second chance at a near-normal life. Here an organ is being prepared for transplantation.



Hematologic Diseases

Hemochromatosis is inherited as an autosomal recessive genetic disorder; that is, individuals receiving the hemochromatosis gene from both parents have a strong likelihood of manifesting the clinical disease. The disorder is characterized by a failure of the normally effective selective limitation of the absorption of dietary iron. The patient exhibits a progressive tissue iron overload resulting in skin pigmentation, cirrhosis of the liver, diabetes (in 50 to 60 percent of patients), and progressive cardiomyopathy. The disease is ultimately fatal. A simple laboratory test has been developed to determine the percent saturation of transferrin, which

can identify individuals at risk before any clinical manifestations of the disease and before any significant iron-loading of the body organs occurs. Using this test, a large-scale prospective screening study was performed in 11,056 healthy Caucasian Red Cross blood donors, which found between 6 and 7 positive individuals per 1,000 male subjects screened and 3 positives per 1,000 women. It is postulated that iron loss through menstruation, childbearing, and lactation is sufficient to explain the lower numbers for female patients. Ideally, this simple screening test will be used before the iron-loading and the resulting organ damage take place and clinical symptoms appear.

Program Highlights

Epidemiology Program

- RFP's were issued for the "Consolidated End-Stage Renal Disease (ESRD) Data System for the Epidemiological Surveillance of ESRD Treatment in the United States." The ESRD data system will collect and analyze information on the incidence, prevalence, and mortality of kidney failure in the United States. The new system will consolidate data from the Health Care Financing Administration, Veterans Administration, Department of the Army, independent transplant and dialysis organizations, and ESRD patient support groups.
- In a collaborative effort, the Epidemiology Program staff helped design the interview and examination sections of the kidney and urologic component of NHANES III.

Renal Physiology/Cell Biology Program

Thirteen center applications were received in response to the RFA for Kidney and Urological Research Centers by the deadline of December 12, 1986. Six George M. O'Brien Kidney and Urological Research Center Awards were issued, with an effective beginning date of August 1, 1987.

Conferences

- The "Fourth International Workshop on Ammonia-genesis" convened in conjunction with the 10th International Nephrology Congress, July 26-31, 1987.
- A conference on the "Control of Renal Growth" was held March 7-8, 1988.

Chronic Renal Disease Program

- A Workshop on "Reuse of Hemodialyzers and Other Related Equipment" convened in Bethesda, Maryland, on May 19, 1987.
- A Long-Range Plan for the Comprehensive Study of Kidney Disease of Diabetes Mellitus has been developed.

- A collaborative effort was launched with the Division of Diabetes, Endocrinology, and Metabolic Diseases to study the natural history of kidney disease in diabetes mellitus in a well-characterized diabetic patient population as part of NIDDK's ongoing DCCT.
- Proposals received in response to the RFP entitled "A Comprehensive Study of Diabetic Renal Disease in the Pima Indian Population" were reviewed with selection of a Data Coordinating Center and a Renal Function Research Laboratory. The study was started in February 1987.
- RA's were issued in FY 1987 and FY 1988 to stimulate proposals on kidney disease of diabetes mellitus to include basic, clinical, and epidemiological studies.



NIDDK-supported research has resulted in significant advances in kidney transplantation and in marked prolongation of the effective life and function of the transplanted organ.

MDRD Program

The Cooperative Clinical Study of Effects of Dietary Modification on Progression of Renal Disease (MDRD Study) is successfully progressing through the Feasibility Phase. Restriction of dietary protein and phosphorus represents the primary intervention; glomerular filtration rate will be the primary outcome measure.

ESRD Program

Recently, all grants and issues pertaining to ESRD were consolidated under the ESRD program. A major accomplishment during this year was the ESRD Therapeutic Intervention Conference held on January 24-25, 1988, highlighting recent advances in therapy for ESRD and focusing on future research plans.

HIV Program

Requests for Grant Applications (RGAs) were issued in February and March 1988 to study the mechanisms underlying genitourinary tract manifestations of HIV

and to determine the effects of HIV infections on the kidney and in dialysis and renal transplant patients. Twenty-two applications were received and reviewed. It is anticipated that several of these will be funded.

A separate RGA was issued in April 1988 in conjunction with NHLBI to study the effect of HIV on the hemopoietic system. Forty-six applications were received and will be reviewed soon.

Urology Program

- Following the NIDDK Workshop on Interstitial Cystitis, August 28-29, 1987, further efforts are being made to advance knowledge and understanding of the incidence and prevalence of interstitial cystitis in the United States and diagnostic criteria for interstitial cystitis. An RFP for research on the urinary tract, including interstitial cystitis, was published early in FY 1987, and DKUH is funding new research projects in interstitial cystitis.
- In response to the PA on Sexual Impotence, several applications were submitted.
- A conference on BPH was held in April 1985. As a result, new proposals were funded. Two groups subsequently reported on the isolation of a prostate growth factor.
- An RFA on growth factors in the kidney, prostate, and hematological systems was published in FY 1987, and a new RFA is being issued in FY 1988.

Division Communications. DKUH continues these efforts through a quarterly column devoted to DKUH activities in both the *American Journal of Kidney Diseases* and the *Journal of Urology* and through regular articles in the National Kidney Foundation Newsletter.

National Kidney and Urologic Diseases Information Clearinghouse. The clearinghouse serves as an information resource for professional and patient education in kidney and urologic diseases through direct response and referral; collects patient and professional educational materials for a subfile on CHID; serves medical and allied health professionals, patients, and the public; and will publish and distribute factsheets, annotated bibliographies, and other educational materials.

The clearinghouse offers the following publications: Understanding Urinary Tract Infections; Prevention and Treatment of Kidney Stones; Age Page: Urinary Incontinence; Age Page: Prostate Problems; Benign Prostatic Hyperplasia Vol. II; 1987 Kidney, Urology, and Hematology Special Report; and MDRD Referring Physician's Handbook.

Committee Activities. Two new committees mandated by Congress have been appointed and have had several meetings in FY 1987.

- The National Kidney and Urologic Diseases Advisory Board is developing a national plan concerning research, training, and patient care needs in diseases of the kidney and lower urinary tract.
- The Interagency Coordinating Committee for Kidney, Urology, and Hematology is in the process of surveying federally supported research in kidney disease and urology. Hematology research is the subject of future meetings.

Hematology Program

- A meeting on Erythropoietin and Chronic Renal Failure was held in Bethesda on March 3, 1987, to discuss research issues growing out of the recent availability of human recombinant erythropoietin and its initial successful use in clinical trials in renal dialysis patients.
- An RGA was issued in December 1986 for research into the molecular mechanisms of the interaction of erythropoietin and its receptor and subsequent cellular signaling.
- A program review in collaboration with the American Society of Hematology reached a consensus that five areas should be singled out for special attention: growth factors, membrane assembly, heme biosynthesis, neutropenia, and AIDS.



A metabolic abnormality can result in urine supersaturated with calcium. Under the right circumstances, insoluble calcium salts will precipitate and form kidney stones.

Program Development Activities for FY 1988

Planned PA initiatives include Individual National Research Service Awards in Hematology and a Request

for Research in Specific Areas of Interstitial Cystitis, which was suggested by an August 1987 workshop.

Planned conference/workshop initiatives include:

- Conference on Renal Growth.
- Regulation of Porphyrin Metabolism: A Molecular Genetic Approach to the Pathogenesis of the Porphyrrias.
- Clinical/Experimental Kidney Transplantation.
- Kidney Disease in Minority Populations.
- Refinement of Management Strategies in ESRD Treatment.
- Kidney Disease of Diabetes Mellitus Update.
- IgA Nephropathy Planning Workshop.
- Hypertension and the Kidney Planning Workshop.
- Cyclosporin A Update: NIDDK Concerns.
- AIDS Nephropathy Planning Workshop.
- HIV in the Dialysis Populations and Other Issues.
- Nutrition in Renal Patients Planning Workshop.
- Conference on Infection and Virulence Factors of the Urinary Tract.
- Hematologic Sequelae of HIV Infection.
- Kidney Stone Prevention and Intervention: Publication of the Proceedings of the 1988 Consensus Conference on this topic.

Workshops also are planned on Epidemiology of Chronic Renal and Urologic Diseases and on Epidemiology of Hypertensive Renal Disease.

Other program initiatives include:

- Sequential Implementation of the Kidney Disease of Diabetes Mellitus Long-Range Research Plan.
- Erythropoietin: Cellular Origin and Gene Expression and Regulation.
- New Approaches to Elucidate the Pathogenesis of Autosomal Dominant Polycystic Kidney Disease.
- Research on Benign Prostatic Hyperplasia.
- Refinement of Management Interventions for the Treatment of ESRD.
- Epidemiology of Interstitial Cystitis.
- Lower Urinary Tract Involvement in HIV Infection.
- HIV Infection in the Renal Hemodialysis Population.

- Renal Disease Resulting from HIV Infections Leading to ESRD.
- Pathobiology of Bone Marrow Suppression in AIDS or AIDS-Related Complex.

Summary and Outlook

The NIDDK conducts and supports research on many of the most serious diseases affecting public health. These diseases constitute a tremendous drain, both direct and indirect, on the human and economic resources of the United States, and no subgroup of our population is immune to their attack.

Institute efforts are planned and coordinated through an extramural support program that provides funding for research at universities, clinical facilities, and research institutions across the country and abroad and an intramural component, which focuses on research conducted primarily within NIDDK's laboratories and clinical facilities on the NIH campus and in Arizona.

The administrative and advisory activities of the Institute are organized to provide programmatic guidance and fiscal, analytical, and review services to facilitate a maximal research effort. Activities aimed at developing and sustaining active linkages to the scientific and health care communities also fall within the Institute's scope of responsibilities.

NIDDK programs encompass a multidisciplinary effort with major emphasis on an optimal mix of basic studies, epidemiologic and clinical research, and research training. The focus on basic research that has traditionally guided NIDDK's programs is grounded in the fact that a fundamental understanding of the intrinsic nature of each disease is imperative for the development of effective strategies for prevention and therapy and that the work of the Institute involves many chronic and progressive diseases with as yet unknown etiologies. Advances in basic knowledge are continually and productively expanded into appropriate clinical and population-based studies and trials and into programs of technology transfer and information dissemination to the community of biomedical researchers, to the practicing physician, and to the public to contribute promptly to the improvement of the Nation's health.

Considerable progress has been made since the last Biennial Report. We hope that the research advances of the past 2 years, only a few of which could be touched upon in this report, will contribute substantially to the creation of new knowledge that will make possible improved diagnosis, treatment, and prevention in the areas of the Institute's research responsibility.

Diabetes Research and Training Centers Program

Introduction

As a result of recommendations by the National Commission on Diabetes, the first Diabetes Research and Training Center (DRTC) grants were awarded in September 1977 in conformity with authorizing legislation (Public Law 93-354). At present, there are six DRTC's located at Albert Einstein Medical College (Bronx), University of Chicago (Chicago), University of Indiana School of Medicine (Indianapolis), University of Michigan Medical School (Ann Arbor), Vanderbilt University (Nashville), and Washington University (St. Louis).

DRTC's are evaluated continually through several varied but complementary processes. These include NIH peer review, program review by NDAB, staff review of progress reports, staff visits to centers, special evaluation projects by Institute staff, scientific merit review of annual meeting presentations and published research results in scientific journals, and in-house evaluations by centers themselves.

Center Features

The basic requirement for establishment of a DRTC is excellence in biomedical research as evidenced by a substantial base of high-quality, NIH-funded research projects. Resources furnished by center funding allow for enhancement of collaborative and multidisciplinary endeavors, from basic and clinical research to the transfer of new knowledge through training of primary care health professionals. In view of these basic DRTC characteristics, this report will focus on new research- and training-based efforts by the centers as well as on center evaluation.

A major advantage of DRTC funding to the recipient diabetes centers is the establishment of shared resources (cores) for use by center investigators. Funds also are provided for a limited number of modest research projects, pilot and feasibility research studies, and other activities to enhance the centers' research and training programs. The cores provide services to funded investigators whose area of research or training interest is diabetes or a related field of the biomedical sciences. These combined resources allow for greater efficiency, better quality control, and greater cost-saving through bulk purchase and foster collaboration and multidisciplinary efforts. Funds for pilot and feasibility studies of modest amounts and limited duration are provided following peer review to young investigators lacking individual support. Also, pilot and feasibility funding is provided either to established

investigators from other fields who are interested in diabetes research or to established diabetes researchers with innovative ideas for new research directions. In addition, a small amount of funding is allowed to enhance the multidisciplinary environment through seminars, conferences, and exchange of information with consultants and lecturers from outside the center institution. DRTC's have provided accordingly for the consolidation of common interests and activities of basic and clinical scientists, practicing physicians, nurses, nutritionists, and other diabetes health care professionals.

NIH Peer Review

During FY's 1986-87, there were 10 diabetes centers competing for continued funding. The result of this competition was the funding of six DRTC's and three Diabetes and Endocrinology Research Centers (DERC's). Each center submitted a detailed application that summarized the progress it had made during the previous project period. Each application was then reviewed by a special initial review group of 10 to 14 expert consultants who conducted a 1- to 2-day project site visit at the center to evaluate in detail each component of the application. A written summary of the findings and recommendations from each site visit team was then provided to the National Diabetes and Digestive and Kidney Diseases Advisory Council for final review and approval. Only centers recommended for support with the highest enthusiasm receive funding. This peer review process ensures that each center is subjected to a rigorous and objective external evaluation of scientific and technical merit at least once every 5 years.

Special Evaluations Undertaken in FY's 1986-87

Although evaluation is a process that is ongoing at all times for the centers, in FY's 1986-87 an evaluation was conducted by the National Diabetes Advisory Board (NDAB). NDAB's update of the "Long-Range Plan to Combat Diabetes" (proposed by the National Commission on Diabetes in 1976) was published in September 1987. It includes a very intensive look at the progress and accomplishments of the DRTC's, their role as a national resource, and recommendations for future directions. An NDAB meeting was held at one center so Board members could review first hand the functioning of a typical center. Based on NDAB's evaluation, the new long-range plan recommends that \$9 million be allocated to NIDDK to enable existing

DRTC's and their sister DERC's to be funded at the full level recommended by the review committees and to support four new centers.

Center Activities

The DRTC's have two main thrusts: biomedical research and training and/or education of health care professionals involved in treatment and management of people with diabetes.

Advances in Biomedical Research

Major advances in biomedical research have been supported during 1986 and 1987 by the DRTC's.

At the Washington University DRTC, studies originally supported by pilot and feasibility funds and now independently funded suggest that insulin-producing beta cells dispersed from rat islets of Langerhans have metabolically regulated K⁺ channels. These studies are important in providing a foundation for a better understanding of islet physiology and pharmacology in models of obesity and diabetes and in furthering our understanding of the mechanism of action of the blood sugar-lowering sulfonylurea pharmacologic agents. These studies also dovetail with transplantation biology studies of the effect of immune modulators that are potentially important regulators of insulin secretion.

At the University of Chicago DRTC, NIH-supported research facilitated by the DRTC cores demonstrated that the replacement of specific amino acid residues within the insulin molecule decreased insulin biological activity by nearly 99 percent. Surprisingly, however, the negative effect of the amino acid substitution could be reversed by deletion of the carboxy terminal end of the insulin beta chain subunit. In part, these results provide a basis for understanding the low biological potency inherent in mutant human insulins. Specifically, they provide insights into the molecular flexibility of insulin and the potential for concerted conformational changes in insulin and its receptor. This new understanding will help to model the mechanisms by which insulin transmits its transmembrane signal and affects intracellular processes.

Studies at the University of Michigan DRTC, through pilot and feasibility funding and center cores, have examined the molecular mechanisms by which insulin alters gene expression. A drug-induced diabetic model has been used to investigate the effects of insulin on synthesis of the pancreatic enzyme amylase. The results of these investigations show that the rat genome contains two genes for amylase. The rate of amylase synthesis by one of these genes was selectively reduced in diabetic animals but restored toward normal by insulin treatment. Subsequent efforts have demonstrated

that the difference in insulin responsiveness of expression of the two pancreatic amylase genes is determined by genetic sites closely linked to genes for the enzyme. Thus, an action of insulin upon gene expression has been defined and will likely lead to identifying the DNA sequences that mediate the induction of specific genes by insulin. Recent efforts have led to the cloning of the two pancreatic amylase genes. This should provide an opportunity to define the precise DNA sequences that mediate the induction of the insulin-dependent amylase gene.

Advances in Training and/or Education

Advances in the transfer of new knowledge through training have occurred at each of the DRTC's. Two examples are presented here.

The University of Chicago DRTC has developed a standardized patient protocol to be used in training medical students in diagnosis and management of patients with diabetes. A standardized patient is an individual who is trained to present simulated history and physical findings consistent with a particular medical complaint or problem. Standardized patients are used to give medical students experience in taking a medical history, conducting a physical examination, and developing and presenting a management plan to the patient. The significance of the studies conducted on the use of standardized patients in diabetes is that the traditional clinical experience for medical students varies depending upon the types of patients that are in the clinic during the time of their rotation. Because of this, some types of patients may never be seen by a student. The use of standardized patients in the DRTC is intended to enhance the traditional clinical experience with the introduction of this innovative system of teaching and evaluating clinical skills.

At the Vanderbilt DRTC, a main focus of the training component has been to improve diabetes patient care through improvement of the patient education process. Activities relating to this goal include development and validation of methodologies to assess educational methods and outcomes, development of innovative instructional strategies and materials, and development of training programs to improve the teaching skills of health professionals. Toward this end, a training program, "Effective Patient Teaching," has been developed for all health professionals. Research and observation led to generation of a list of 19 specific teaching skills believed to be required of health professionals, specifically those devoted to diabetes care. The program is 4-1/2 days in length, and evaluation of the program is ongoing. About one-half of the program is devoted to didactic presentations of the important teaching skills; in the other half,

participants practice teaching skills in small group sessions. All practice teaching sessions are videotaped for later review. Each participant also receives a 75-page notebook for subsequent use.

Collaborations

DRTC's have established collaborations within their own group and with Federal and private agencies and organizations with missions relating to education and training in diabetes. Active collaborations currently exist with Federal agencies (e.g., Centers for Disease Control and Indian Health Service), professional and voluntary health organizations (e.g., American Diabetes Association, Juvenile Diabetes Foundation, American Association of Diabetes Educators), state and city health

departments, local colleges, local hospitals, other voluntary organizations, and community health centers.

Conclusion

This report briefly addresses the extent to which DRTC's have fulfilled the original goals set for them by the National Commission on Diabetes. New developments since the last report are described and indicate the great potential for DRTC's in stimulating progress in research and education related to diabetes. The DHHS finds that the DRTC's are continuing to progress toward achievement of their objectives and views them as a national resource for progress in research and education related to diabetes.

Digestive Diseases and Nutrition Centers Program

Introduction

The Division of Digestive Diseases and Nutrition (DDDN) Centers Program was initiated in 1979 with the award of five Clinical Nutrition Research Units (CNRU's) and expanded in 1984 with the award of six new Digestive Diseases Core Center (DDCC) grants. The centers program has evolved over the past decade, expanding to a total of 17 centers: 5 CNRU's and 12 DDCC's. The center grants are 5-year awards. The numbers of CNRU's and DDCC's have remained relatively constant over the past several years. Funds that become available as existing grants complete their award period are competed for openly through published requests for applications. The DDDN centers program provides support for research centers at institutions where there is an existing base of excellent biomedical research and where it can be demonstrated that the use of shared resources will lead to cooperative and collaborative research efforts, leading to enhanced efficiency and low-cost routine services, new cooperative and collaborative efforts among investigators, providing services and resources hitherto unavailable to investigators on a routine basis, and expanding the capabilities and potential for research accomplishments greater than that possible through individual projects.

Digestive Diseases Core Centers

Biomedical Research Component

The biomedical research component at DDCC's focuses on research areas such as liver disease; abnormal liver metabolism; problems related to liver transplantation; cholesterol gallstone disease; Crohn's disease and inflammatory bowel disease; normal and

abnormal gastrointestinal motility; infectious diarrheal diseases; and absorption, secretion, and regulatory processes in the gastrointestinal tract. Research at all centers is directed toward enhancing the understanding and knowledge of digestive diseases leading to improvement in the care of patients with these conditions.

Biomedical Core Facilities

The biomedical research core at DDCC's provides center investigators with shared resources to conduct biomedical research in an efficient and cost-effective manner. Among the benefits from these shared resources are a greater potential for collaboration, availability of expert consultation and use of state-of-the-art facilities, lower cost for services rendered, and the means to pursue limited pilot and feasibility research.

Core facilities at DDCC's have included conventional transmission electron microscopy, freeze-fracture electron microscopy, light and electron-microscopic immunocytochemistry, light and electron-microscopic autoradiography, electron-microscopic histochemistry, electron-microscopic lectin probe studies, cell culture facilities, and laboratory animal facilities.

Pilot and Feasibility Studies

The core center grant mechanism provides for support of a limited number of innovative pilot and feasibility research projects that relate to the center's overall research focus. As the name suggests, these projects are supported to test new hypotheses, provide opportunities for new collaborations, and explore new methods or procedures as they apply to research problems in digestive diseases. These studies, when fruitful, lead to research and grant applications for fuller exploitation of the initial concept.

Clinical Nutrition Research Units

Advances in the knowledge of human biochemistry and physiology have placed clinical nutrition on a sound, scientific base. Many nutritional deficiency states, consequences of inborn errors of metabolism, and diet-related diseases are now understood and may be treatable or preventable. However, there remain many unanswered questions on the relationship of diet to health and disease, chronic diseases, and aging.

Advances in research to help answer questions about nutrition and disease are derived from many disciplines such as biochemistry, molecular biology, genetics, and physiology and from medical specialties such as internal medicine, pediatrics, and surgery. Nutrition science is interdisciplinary and complex and is dependent upon the close interaction among research investigators, health service providers, and educators. As a means of encouraging a multidisciplinary approach to clinical nutrition research, DDDN is part of an NIH-wide program of CNRU support. Specific objectives of a CNRU are (1) to create or strengthen foci in a biomedical research institution for multidisciplinary research in clinical nutrition to develop new knowledge about specific nutrients in health throughout the life cycle and in the prevention and treatment of disease; (2) to strengthen training environments to improve the education of medical students, house staff, practicing physicians, and allied health personnel in clinical nutrition; and (3) to enhance patient care and promote good health by focusing attention on clinical nutrition and generating nutritional information for the public.

The essential components of a CNRU are (1) research with human subjects and populations; (2) laboratory investigations; (3) research training; (4) shared facilities and research services; (5) education programs for medical students, house staff, practicing physicians, and allied health personnel; (6) research components of nutritional support services; and (7) public information activities.

CNRU Research Core Facilities

Core facilities of CNRU's are developed to support research in the broad areas of fundamental and clinical nutrition. Application of state-of-the-art techniques in the areas of cell biology, molecular biology, immunology, and integrative physiology is encouraged to increase knowledge concerning function and requirements of nutrients, relationship of diet (and nutrients) to health and disease, and prevention and treatment of diseases as an outgrowth of nutrition research.

Fundamental research supported by NIDDK generally has been nutrient centered rather than focused on a particular disease, organ, or life cycle. In contrast, clinical investigations usually concern problems interrelating nutritional status with the biochemical and physiological function of a cell population, organs, or the whole individual.

Assessment and Evaluation

In 1984, the National Digestive Diseases Advisory Board (NDDAB) held a workshop to explore possible mechanisms for evaluating and monitoring DDCC's. NDDAB suggested criteria and mechanisms for monitoring programmatic activity and suggested methods of obtaining evaluation information, including the adoption of a standardized reporting method.

In October 1985, digestive diseases center directors met to consider and comment on a standardized format developed by NIDDK for reporting information from the centers. A similar meeting of CNRU directors was held in January 1986 for the same purpose. The reporting format developed at these meetings is used in conjunction with the annual progress report required from each center.

In February 1988, DDCC and CNRU directors met with DDDN and senior NIDDK staff to consider the development of guidelines for the centers and related issues. NIDDK has completed the preparation of formal administrative guidelines for DDCC's and CNRU's as a product of this meeting.

Summary

The DDDN centers program provides the assessment mechanisms and reporting procedures that, in concert with the NIDDK peer review process, have supported a highly effective community of research centers of excellence. The role of DDCC's and CNRU's is to improve the understanding of the causes of digestive diseases and of nutritional metabolism in healthy and diseased states. It is this understanding that will lead to improved methods for early detection, diagnosis, and treatment of digestive diseases and nutritional disorders with consequent improved patient care and lower health care costs. DHHS finds that the DDDN centers program continues to progress toward its objectives and views it as a national resource for progress in its special research and training areas.

Kidney and Urologic Diseases Research Centers Program

Introduction

The Kidney and Urologic Diseases Research Centers (KURC's) Program was initiated in September 1987, when the awards were granted.

In its report on the FY 1986 budget for the Department of Health and Human Services, the House Committee on Appropriations stated:

The center concept might provide the necessary framework and mechanism for the kidney-urology community to intensify the research advances to prevent dialysis and transplant treatment for many citizens. The committee requests an evaluation of the proposal to establish up to six multidisciplinary, inter-institutional kidney-urology centers to be funded after employing the usual and customary processes of the National Institutes of Health to insure the quality and scientific merit of the proposals received. Those centers would be: hypertension and the kidney, obstructive and hereditary diseases of the urological system and the kidney, nutrition and the kidney, and cellular injury and the kidney (House Report No. 99-289, p. 51).

In evaluating the centers concept, NIH recognized that Public Law 99-158, the Health Research Extension Act of 1985, gave NIDDK the authority to "provide for the development and substantial expansion of Centers for Research in Kidney and Urologic Diseases." Thereafter, NIH proceeded to evaluate the scientific and potential benefit of establishing a kidney and urologic diseases research centers program within NIDDK, the Institute with primary responsibility for research efforts in these fields.

The goal of such a centers program would be the reduction of the major causes of kidney and urologic diseases by the early 1990's. The proposed program was to focus on end-stage renal disease (ESRD) and benign prostatic hyperplasia (BPH). As the U.S. population ages, both of these diseases are increasing in frequency. ESRD and BPH have combined annual costs in excess of an estimated \$4 billion, and their costs are increasing steadily. Intensification of research on these diseases through a centers mechanism could reduce by approximately 20 percent the number of patients entering the Federal ESRD program or requiring therapies for BPH, at an estimated savings of \$1 billion annually.

Current treatment approaches to ESRD and BPH are only palliative because they deal solely with the

complications of already fully established disease processes. For ESRD, available therapies are kidney dialysis or transplantation. For BPH, surgical techniques are used to remove or pare glands that have become pathologically enlarged. In both cases, current methods of clinical management are expensive and do not offer either prevention or cure.

At the same time, emerging research opportunities in kidney and urologic diseases offer considerable promise of generating new knowledge to combat ESRD and BPH through strategies aimed at early diagnosis and prevention. Each of the areas in which centers were proposed was seen as offering compelling research challenges and opportunities that could be pursued effectively through the centers mechanism under consideration.

NIH experience with specialized research centers suggested that the centers could provide a valuable means of focusing investigations on a given topic or disease. The proposed centers were seen to aim at fostering multidisciplinary and interdisciplinary research efforts, which would complement the regular research grant mechanism by attracting a greatly needed cadre of new biomedical research investigators to the kidney and urologic diseases fields.

In evaluating the feasibility and potential benefits of establishing KURC's, the following were considered: the magnitude of the health problems such centers would address, the state of research and treatment, research opportunities that centers might pursue, specific research emphasis of possible centers, expertise and interest of potential center grant applicants, beneficial characteristics of the centers approach, recommendations of professional and voluntary organizations in the kidney and urology fields, and the referred authorizing legislation related to the centers concept.

Based on the evaluation of these considerations, there was sufficient reason to believe that the proposed KURC program was scientifically feasible and that it would contribute positively to advances in research knowledge and therapeutic approaches relative to ESRD and the underlying mechanisms and causes leading to BPH.

Areas for Specific Research Emphasis

Areas selected for specific research emphasis for KURC's were to focus on the major causes of ESRD and BPH: hypertension, diabetes mellitus, obstructive and

hereditary diseases of the urologic system and the kidney, nutrition and nephrotoxins, immunologic renal disease, and renal failure resulting from cell injury.

Centers Description

Six KURC's were established in September 1987 to conduct biomedical research. These KURC's are located at Brigham and Women's Hospital, Boston, Massachusetts; Research Foundation of the State University of New York, Syracuse, New York; Northwestern University, Chicago, Illinois; Vanderbilt University, Nashville, Tennessee; University of Alabama, Birmingham, Alabama; and University of Michigan, Ann Arbor, Michigan.

Brigham and Women's Hospital Kidney and Urology Research Center is a comprehensive, multi-institutional, interdisciplinary center where research efforts are devoted to studies of diabetes mellitus and the kidney and nephrotoxicity/toxic cell injury. Four other institutions, operating under a consortium arrangement with Brigham and Women's Hospital, also participate: Beth Israel Hospital, Massachusetts General Hospital, Joslin Diabetes Center, and Tufts New England Medical Center. Dr. Barry M. Brenner serves as center director.

The Research Foundation of the State University of New York at Syracuse Kidney and Urology Research Center focuses its research efforts on defining the pathogenetic mechanisms of vesical, ureteral, and renal dysfunctions in obstructive uropathy through biochemical, morphologic, and functional studies. Research activities are conducted at three different institutions: SUNY at Syracuse, University of Michigan at Ann Arbor, and University of Pennsylvania at Philadelphia. Dr. Ahmad Elbadawi, at SUNY, serves as center director.

The Northwestern University Kidney and Urology Research Center concentrates its research efforts on the study of cellular and chemical aspects of BPH. The basic thrust of this center is to elucidate the mechanisms responsible for BPH, utilizing in vivo and in vitro models. Dr. John T. Grayhack serves as center director.

The Vanderbilt University Kidney and Urology Center's main objective is to study the cellular basis of renal immune injury to define the basic putative mechanisms resulting in progressive glomerular sclerosis. Dr. Harry R. Jacobson serves as center director.

The University of Alabama Kidney and Urology Research Center conducts basic and clinical research studies on the mechanisms and consequences of renal disturbances associated with or stemming from renal hypertension. The underlying theme of this center is that essential hypertension is secondary to a primary renal disturbance that leaves the kidney with an impaired capacity to adjust sodium excretion to intake in the normotensive state. Dr. Robert G. Luke serves as center director.

The University of Michigan at Ann Arbor Kidney and Urology Research Center's goal is to bring together the varied expertise and approaches of senior scientists working primarily outside the renal area to interact with individuals with a nephrology background and to focus such integrated expertise on mechanisms of glomerular injury and, in particular, on the sequence of events leading from initial immune- or nonimmune-mediated glomerular injury to sclerosis of the glomerulus and on how renal tubules are damaged by immunologic and inflammatory mediators. Dr. Richard L. Tannen serves as center director.

Summary

Public Law 99-158, the Health Research Extension Act of 1985, gave NIDDK the authority to provide for the development and substantial expansion of centers for research in kidney and urologic diseases. NIDDK, through its DKUH, opened a national competition to establish a limited number of KURC's to investigate the epidemiology, causes, prevention, and treatment of kidney and urinary tract disorders. Six centers that demonstrated significant potential for successful research were established in September 1987 and are actively pursuing studies toward achievement of the goal of preventing, reducing, or eliminating the major causes of specific kidney and urologic diseases by the early 1990's.



*National Institute of
Diabetes & Digestive &
Kidney Diseases*

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